ORIGINAL ARTICLE

Clinico-Pathological Analysis of Medulloblastoma at a Tertiary Care Centre- A Retrospective Study

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ABSTRACT

Introduction: Malign ant brain tumors are the leading cause of cancer death among paediatric patients, and medulloblastoma (MB) is the most common malignant neuroepithelial tumor in this age group. It is treated by complete surgical resection followed by chemotherapy and neuraxis radiotherapy. In spite of the improving survival rate, survivors succumb to treatment-induced side effects. To reduce toxic effects, targeted treatment based on histological subgroups is proposed.

Aims and objectives: This study was undertaken to identify the prevalence, clinical features, and histological spectrum of MB as well as frequency of each subgroup of MB.

Results: Of 60 patients, 45 (75%) were male and 15(25%) were female. Age of patients ranged from 7 months to 65 years with a mean of 15.88 ± 15.83 years. Fifty six patients (93.3%) had vomiting, fifty patients (83.3%) had headache. In forty two patients tumour was located in midline while remaining 18 patient's location was in cerebellar hemispheres. Of the 60 patients; 36 (60%) were diagnosed as Classical variant constituting the major part. This was followed by desmoplastic, medulloblastoma with extensive modularity, large cell/ anaplastic variant in 23.33% (14 subjects), 10% (6 subjects) and in 6.67% (4 subjects) respectively.

Conclusion: Combined evaluation of histopathological features of patients with medulloblastoma, should be used for risk stratification and can be targeted in this aggressive disease to avoid the side effects of chemo radiotherapy.

Keywords: Histological subgroups; Malignant neuroepithelial tumor; Medulloblastoma.

INTRODUCTION

Medulloblastoma (MB) is the most common embryonal tumour and the most malignant CNS tumour arising in childhood. It represents nearly 33% of paediatric and 1% of adult brain tumours and is associated with high morbidity and mortality[1]. In children it comprises approximately one quarter of all intracranial tumours, arising predominantly from the cerebellar vermis and primarily affecting children in the first decade of life with a peak age of 7 years, having a slight male predilection[2]. It can locally infiltrate the brain stem and/or the fourth ventricle and may spread along the Cranio- spinal axis. The newest classification scheme seperate MB into two separate general designations, MB, histologically defined and MB, genetically defined[3]. Histologically, MB can be segregated into variants including classic, desmoplastic/ nodular (DN), MB with extensive modularity (MBEN) and large cell/anaplastic (LCA)[3,4]. Medulloblastoma, genetically defined is sorted out into WNT-activated, SHH activated and TP53-mutant, SHH-activated and TP53-wild-type, and non-WNT/non-SHH groups. The latter group can be further subdivided to provisional subclasses, group 3 (G3) and group 4 (G4) when the ability to distinguish the two is possible. However, this new classification scheme has brought about challenges

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as to the practical applicability, especially in a resource limited setting like India as in many centers of India molecular analysis cannot be carried out; hence it is not feasible to sort out MB in genetically defined subgroups. Histologically, they can be placed into defined subgroups and that is important because post operative type and intensity of therapy can be individualized according to these subgroups. Hence, current mechanisms for clinical prognostication and stratification include clinical factors (age, presence of metastases, and extent of resection) as well as histological sub grouping[5]. This study was undertaken to identify the prevalence, clinical features, and histological spectrum of MB as well as frequency of each subgroup of MB.

MATERIALS AND METHOD

This is a retrospective type observational study conducted in our department during the period 2017-2019. All the patients diagnosed as medulloblastoma (60 cases) were included. Clinical data like age, sex, chief complaints, and radiological details were collected in a predesigned and semi-structured per-forma. Histopathological examination of all specimens was done. Very small tissue, other neoplastic & non-neoplastic brain lesions, cases with incomplete history and radiological details and autolysed tissue specimen were excluded from the study.

Statistical analysis:

The findings were tabulated in Microsoft Excel Worksheet and analysed by using the Standard Statistical Package for the Social Sciences (SPSS) version 20.0 for windows. Quantitative data was presented as mean and standard deviation. Qualitative variables were presented as frequencies and proportions.

RESULTS

Incidence

During the period of two years, a total of 1004 CNS specimens were received for histopathological examination; out of which 60 specimens diagnosed as medulloblastoma in histopathology were included constituting 5.98% of total neurosurgical biopsies.

Demographics

The results of the study revealed a male predominance of 75% (45/60) of the cases in overall MB with a M/F ratio of 3:1. The mean age was 15.88 ± 15.83 years with an age range of 7 months to 65 years. The youngest was <1 year and the oldest was >60 years. Maximum number of study participants (51.7%) belonged to 1-10 years of age group. [Figure 1]

Presenting complaints

The initial symptom in majority of cases was raised intracranial pressure leading to vomiting (93.3%), headache (83.3%) followed by difficulty in walking (33.3%), restlessness and irritability (25%). Diplopia was present in 12 (20%) subjects and 10 (16.7%) patients presented with papillo-oedema. [Figure 2]

Topographic details

In 42 patients (70%) location for MBs was midline; whereas 18 (30%) subjects tumour was located in cerebellar hemispheres.

Histopathological sub grouping with clinico pathological features

The series of tumours (n 60) was composed of predominantly classical variant constituting 60% (36 cases) of total. It was followed by desmoplastic variant, medulloblastoma with extensive nodularity, large cell/ anaplastic variant in 23.33% (14 subjects), 10% (6 subjects) and in 6.67% (4 subjects) respectively. [Figure 3]

Medulloblastoma, classic

The mean age for cases of classical variant medulloblastoma was 16.83 years with an age range of 4-65 years. Of 36 cases of classical variant; 25 (69.4%) were males while 11 (30.6%) were females. In 27 (75%) patients tumour was in midline and in 9 (25%) cases tumour was located in cerebellar hemispheres.

Classical variant was characterized by extreme cellularity having small undifferentiated cells which were most commonly present in a pattern less sheet arrangement. Occasionally, tumour cells were arranged as pseudo- rosettes about the supporting blood vessels. These small cells having round, oval or carrot shaped nuclei, being variable in size, highly hematoxyphilic, imparting a blue tinctorial quality to histological sections, scanty poorly defined cytoplasm and high nuclear cytoplasmic ratio. Mitosis was frequent. Reticulin was absent or minimal and concentrated around blood vessels. [Figure 4a] In 9 (25%) cases; scant connective desmoplasia and mild anaplasia were noted. Apoptosis was graded into focal (<10%), diffuse (10-50%) and extensive (>50%). In classic variant 23 (63.9%) cases showed diffuse apoptosis, 6 (16.7%) focal apoptosis, and 7 (19.4%) showed extensive apoptosis. Necrosis was seen in 23 (63.9%) cases of total 36 cases of classical variant of MB.

Desmoplastic/nodular medulloblastoma (DN)

Mean age of presentation for desmoplastic/ nodular variant was 11.90 years with an age range of 7 months- 42 years. Of the 14 cases; there was 11 males (78.6%) and 3 (21.4%) females. Tumour location was midline in 10 (71.4%) participants & cerebellar hemispheres in 4 (28.6%) cases.

Histologically desmoplastic/ nodular variant characterized by biphasic appearance in which pale islands of loosely textured tissue containing cells with polar, finely fibrillated processes (nodules of neurocytic cells) surrounded by compact sheets and trabeculae of undifferentiated cells. This pattern was accentuated in preparations stained for Reticulin fibers, wherein Reticulin-free islands of variable sizes (corresponding to the pale islands on H&E sections) were encompassed by zones of tumour that were rich in Reticulin. [Figure 4b] Connective tissue desmoplasia was seen in 100% cases. Necrosis and anaplasia was noted in 3 (21.4%) cases. Desmoplastic/ nodular variant showed diffuse apoptosis in 1 case while 13 cases showed focal apoptosis.

Medulloblastoma with extensive nodularity (MBEN)

In current cohort; there were 6 patients of MBEN with a mean age of 17 years and an age range of 4 to 54 years. Male to female ratio was 5:1. Midline location was in 5 (83.3%) cases while cerebellar hemispheric location was only in 1 (16.7%) patient.

Histologically, it was characterized by dominance of nodules rather than primitive elements. The nodules were irregular, coalesce together and adjacent nodules were connected by linear arrays of neurocytic cells producing a streaming pattern. Similar to other desmoplastic/ nodular tumours, MBENs show Reticulin deposition in the inter-nodular regions. [Figure 4c] All 6 cases showed desmoplasia and focal apoptosis. Necrosis was seen only in 1 (16.7%) case.

Large cell/Anaplastic medulloblastoma (LCA)

There were 4 (6.67%) cases of LCA variant with a mean age of 19.5 years and an age range of 4-60 years. All were in males with a midline location in single case while remaining 3 (75%) tumours were located in cerebellar hemispheres.

Histologically large cell/ anaplastic variant (LCA) is a combination of two variant- the anaplastic variant and the large cell variant. The large cell variant was characterized by large discohesive cells with prominent nucleoli whereas the anaplastic variant was characterized by increased cell size, cytologic pleomorphism, cell molding and wrapping, frequent mitotic activity, and apoptotic bodies. [Figure 4d] None of the case of LC/A variant had showed desmoplasia. All cases showed anaplasia and diffuse apoptosis.

DISCUSSION

Medulloblastoma was first in described 1925, in a series of 31 cases first considered to be an unusual type of glioma arising primarily in the cerebellum of children[6]. It was included in the original histogenetic classification scheme introduced by Bailey and Cushing, in which brain tumours were designated based on the morphologic similarity to cell types in the developing brain[7]. The primitive embryonic tumour was believed to derive from an undifferentiated cell type termed the "medulloblast" multi- potent stem cell thought to be present in neural tube[8].

After leukemia, brain tumour, is the major cause of death in paediatric oncology. Medulloblastoma is the foremost common paediatric malignant brain tumour[9]. MB is also the main reason for cancer-related illness and death among children[10,11]. It develops inside the cerebellum on the posterior part of the brain and rapidly grows. Due to common occurrence, the prevalence and histological variants of MB should be well understood to help in the management of this potentially curable disease as it responds very well to radiation and chemotherapy post surgery. There is a necessity to attain a serious examination, so as not to result in an over or under treatment, which in both cases leads to an excessive death rate[12].

In current cohort, male predominance was noted (M:F 3:1); which was comparable with other studies carried out by Fattet S et al [13], Gowda KK et al[14], Samaka RM et al[15], Ellison DW et al[16], Lamont JW et al[17], Kool M et al[18]. The mean age was 15.88 ± 15.83 years with age range from 0.7 years to 65 years. The mean age was slightly higher than other studies; which could be due to different demographic characteristics of the patients. Majority of patients in our study were children (65%) followed by adults (33.33 %) and 1 infant (1.67%), which is in corroboration to other studies like Silva RD et al [5], Samaka RM et al[15].

Initial presentation in majority of the patients due to tumour was caused by the raised intracranial pressure leading to vomiting and headache; equitable to literature. In majority of the cases (70%) of MB location was central or midline while 30 % were in cerebellar hemispheres.

This was in corroboration with other studies like Samaka RM et al[15], Korshunov A et al[19].

Most common histological variant was classical variant (60 %) followed by desmoplastic / nodular (23.33%), medulloblastoma with extensive nodularity (10 %) and large cell/ anaplastic variant (6.67 %). These results were similar to other studies done by Fattet S et al [13], Samaka RM et al[15], Kool M et al[18], Korshunov A et al[19], and Eberhart CG et al[20].

In current study, mean age for cases of classical variant of medulloblastoma was 16.83 years and male: female ratio was 2.2:1 denoting a male dominance. Comparable results also noted in study carried out by Pramanik P et al [21] where mean age was 13.6 years and male: female ratio was 2.2:1. On analyzing topographical distribution of this variant; 75% tumours were located in vermis (midline) while 25% tumours have hemispheric location; similar to other studies[21].

In our study; apoptosis was present in all cases of classical variant where 48.33% cases showed focal apoptosis, 40% cases showed diffuse and 11.67% cases showed extensive apoptosis equitable to other studies available in literature[2,15,22]. Necrosis was seen in 23 (63.9%) cases; out of 36 cases of classical variant of MB and it was slightly lower than studies done by Giangaspero F et al [23] and Giordana MT et al[24].

For desmoplastic/ nodular variant (14 cases); mean age of presentation was 11.9 years and a male predilection was noted (M: F ratio 3.7:1) comparable to study carried out by Pramanik P et al [21]. In majority of the cases (71.4%) location were midline and 100% cases showed desmoplasia. Necrosis and anaplasia was noted in 3 (21.4%) cases. This variant showed diffuse apoptosis in 1 case while 13 cases showed focal apoptosis.

In present study, there were six cases of MBEN with a mean age of 17 years and male female ratio of 5:1. Desmoplasia and focal apoptosis was present in all cases while necrosis and anaplasia was seen only in a single case.

In LC/ A variant, was predominantly located in cerebellar hemispheres (75%); with a mean age of 19.5 years. All cases showed anaplasia and diffuse apoptosis while desmoplasia was absent.

In current cohort; necrosis was present in 48.33 % cases and absent in 51.67 % cases. These results are similar with studies done by Giangspero F et al [2] and Samaka RM et al [15]. In our study desmoplasia was present in 48.3 % cases while absent in 51.7 % cases.; similar to study done by Samaka RM et al [15] where desmoplasia was present in 51% cases and absent in 49% cases.

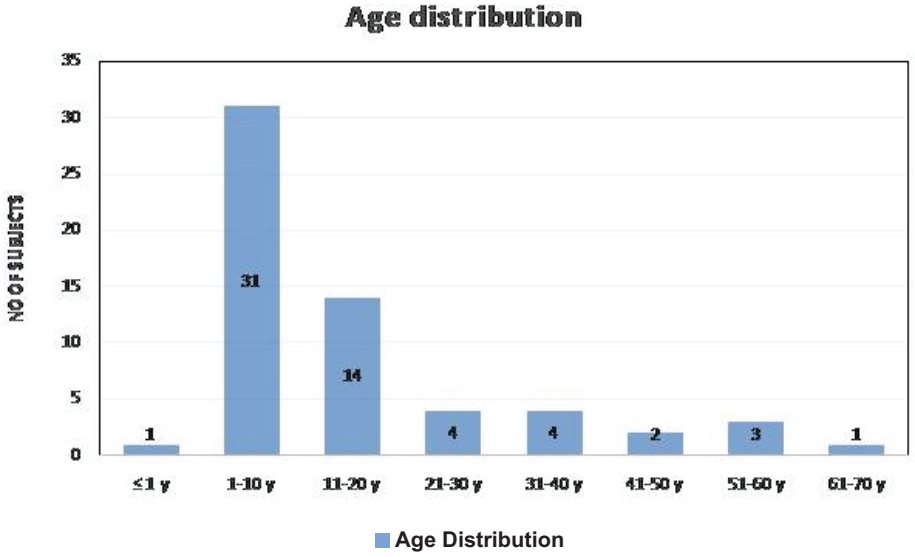

Figure 1: Age distribution of study subjects

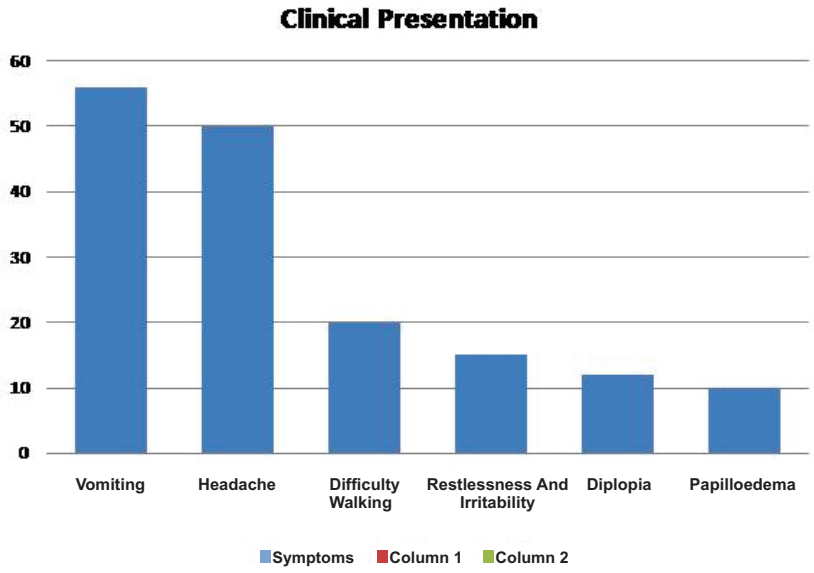

Figure 2: Clinical presentation of study subjects

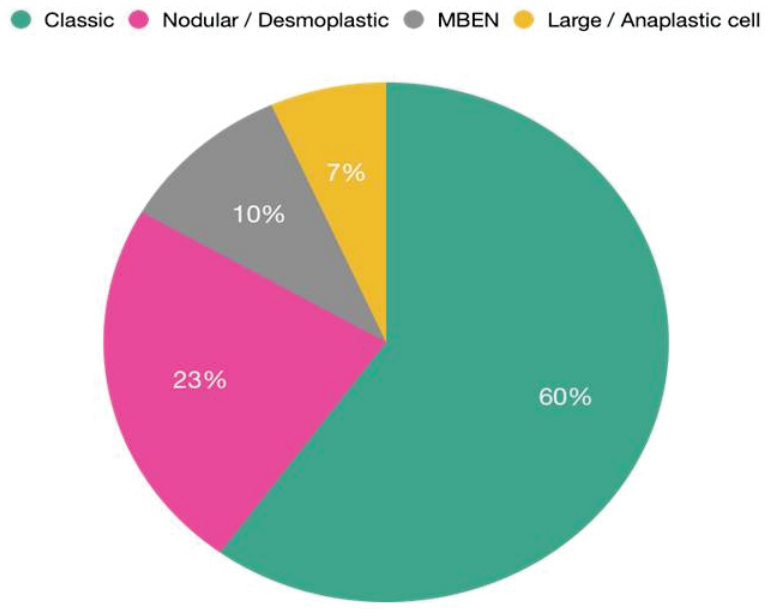

Figure 3: Distribution of histological subgroups in study subjects

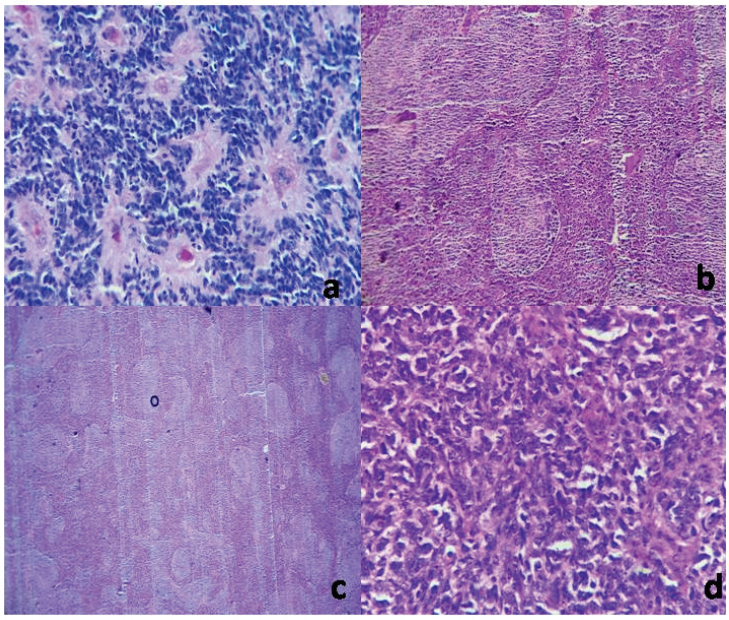

Figure 4: 4a) Microphotograph showing classic variant of medulloblastoma with areas of Homer Wright rosettes; 4b) Desmoplastic/ nodular variant with pale nodules surrounded by intervening hyper cellular inter-nodular areas; 4c) Medulloblastoma with extensive nodularity showing an expanded lobular architecture characterized by large elongated reticulin free zones; 4d) Large cell/anaplastic variant with large polygonal cells, nuclear pleomorphism and prominent nucleoli (H & E; x100, x400)

CONCLUSION

Early diagnosis and treatment is the key to management of medulloblastoma. Each histological variant is usually different in its implicated pathway and pathology. Treatment of these patients should be individualized based on histological variants to reduce the devastating side effects.

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